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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/462,089	05/01/2000	Michael Kerin McNamara	017227/0154	4665

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EXAMINER	
HUYNH, PHUONG N	
ART UNIT	**PAPER NUMBER**
1644	

DATE MAILED: 12/03/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/462,089	MCNAMARA, MICHAEL KERIN	
	Examiner	Art Unit	
	Phuong Huynh	1644	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *Three* MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *15 October 2003*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-8 and 62-83* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-8 and 62-83* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. §§ 119 and 120

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

13)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application) since a specific reference was included in the first sentence of the specification or in an Application Data Sheet. 37 CFR 1.78.

a) ☐ The translation of the foreign language provisional application has been received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121 since a specific reference was included in the first sentence of the specification or in an Application Data Sheet. 37 CFR 1.78.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____.
4) ☐ Interview Summary (PTO-413) Paper No(s). _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other:

DETAILED ACTION

1. A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 10/15/03 has been entered.

2. Claims 1-8 and 62-83 are pending and are being acted upon in this Office Action.

3. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art.to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

4. Claims 1-8, 62-71, and 78-83 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling only for (1) a composition for use in eliciting an effective immune response to LHRH, said composition comprising a LHRH conjugated to diphtheria toxoid and adsorbed to an ionic polysaccharide wherein said LHRH is an amino acid sequence of at least five contiguous amino acids of the C terminal end of SEQ ID NO: 1 selected from the group consisting of SEQ ID NO: 2, SEQ ID NO: 3, SEQ ID NO: 4; (2) the said composition wherein said ionic polysaccharide is DEAE-dextran; (3) the said composition wherein the LHRH is the amino acid sequence of SEQ ID NO: 2; (4) the said composition wherein said ionic polysaccharide is DEAE-dextran; (3) the said composition wherein the LHRH is the amino acid sequence of SEQ ID NO: 4; (5) a pharmaceutical composition comprising a LHRH-diphtheria toxoid conjugate and absorbed to an ionic polysaccharide together with one or more pharmaceutically acceptable carriers and/or diluents wherein said LHRH is an amino acid sequence of at least five contiguous amino acids of the C terminal end of SEQ ID NO: 1; (6) the said pharmaceutical composition wherein said ionic polysaccharide is DEAE-dextran; (7) the said pharmaceutical composition wherein the LHRH the amino acid sequence of SEQ ID NO: 2 and (8) the said pharmaceutical composition wherein the LHRH is the amino acid sequence of SEQ ID NO: 4, **does not** reasonably provide enablement for (1) *any* composition or (2) *any* pharmaceutical composition for use in eliciting an effective immune response to LHRH said

composition comprising *any* LHRH such as (3) *any* LHRH wherein the LHRH is *any* amino acid sequence at least 5 contiguous amino acids of the C-terminal end of SEQ ID NO: 1, (4) *any* "derivative thereof" such as derivatives "comprise" fragments and amino acid substitutions, insertions or deletions of any LHRH that is at least 5 contiguous amino acids of the C-terminal end of SEQ ID NO: 1, and (5) any LHRH up to 10 amino acids in length and comprises at its C-terminal end 5 contiguous amino acids of the C-terminal end of SEQ ID NO: 1, any LHRH derivative comprises spacers introduced at the N-terminus, or any LHRH derivative comprises at least any one amino acid substitution according to Table I for inducing antibody immune response to LHRH for contraception (inhibits the reproductive capacity of the animal). The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in **scope** with these claims.

Factors to be considered in determining whether undue experimentation is required to practice the claimed invention are summarized *In re Wands* (858 F2d 731, 737, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988)). The factors most relevant to this rejection are the scope of the claim, the amount of direction or guidance provided, the lack of sufficient working examples, the unpredictability in the art and the amount of experimentation required to enable one of skill in the art to practice the claimed invention. The specification disclosure is insufficient to enable one skilled in the art to practice the invention as broadly claimed without an undue amount of experimentation.

The specification discloses only a composition or a pharmaceutical composition comprising a LHRH conjugated to diphtheria toxoid and adsorbed to an ionic polysaccharide wherein said LHRH is an amino acid sequence of at least five contiguous amino acids of the C terminal end of SEQ ID NO: 1 selected from the group consisting of SEQ ID NO: 2, SEQ ID NO: 3, SEQ ID NO: 4 for antibody immune response to LHRH for contraception (inhibits the reproductive capacity of the animal). The specification discloses SEQ ID NO: 4 is a derivative of SEQ ID NO: 2 wherein spacers have been introduced at the N-terminus (page 5, lines 22-23). The specification defines derivatives on page 5 to include any fragments, parts, portions, chemical equivalents, mutants, homologs, analogs from natural, synthetic or recombinant source and fusion proteins...chemical equivalents may not necessary derived from LHRH but may share certain similarities.

The specification does not teach how to make, much less how to use any composition or pharmaceutical composition mentioned above because there is insufficient guidance as how to

make any derivative such as fragments of LHRH so long the fragment contains at least 5 contiguous amino acids of the C terminus of SEQ ID NO: 1. The term "comprises" is open-ended. It expands the fragment to include additional amino acids at either or both ends so long it contains the last five amino acids of SEQ ID NO: 1. There is insufficient guidance as to which undisclosed amino acids to be inserted, deleted, substituted and whether the resulting LHRH derivative has the same secondary and tertiary structure as SEQ ID NO: 1. Without the specific amino acid sequence, one of skill in the art cannot make, much less use the derivative in the claimed composition and pharmaceutical composition for inducing antibody response that is specific to LHRH for inhibiting the reproductive capacity of the animals.

With regard to claim 66, even if the derivative wherein the LHRH is up to 10 amino acids in length and "comprises" its C-terminal end 5 contiguous amino acids of SEQ ID NO: 1, there is insufficient guidance what are the "component" in the LHRH that is conjugated to dipheria toxoid and absorbed to an ionic polysaccharide in the claimed composition. Since the "component" in the claimed composition is not enabled, it follows that any composition mentioned above where ionic polysaccharide is DEAE dextran, or wherein said LHRH is SEQ ID NO: 1, 2, 3, or 4 is not enabled.

With regard to claim 78, there is insufficient guidance for the other amino acids in the LHRH amino acid sequence so long the LHRH amino acid sequence is 5 contiguous amino acids of the C-terminal end of SEQ ID NO: 1 in the claimed composition. Let alone inducing any immune response to LHRH, in turn, effective for inhibiting the reproductive capacity of the animals.

As to claims 80-83, since the LHRH derivatives are not enabled, it follows that the spacers and at least one amino acid substitution according to table I in the claimed composition are not enabled. Even if the LHRH derivative is defined, it is not clear as to what "spacers" are being claimed. The specification discloses only SEQ ID NO: 4 is a derivative of SEQ ID NO: 2 wherein the specific spacers have been introduced at the N-terminus (page 5, lines 22-23). Further, there are insufficient in vivo working examples demonstrating that any composition or pharmaceutical composition comprising any derivative of LHRH mentioned above is effective for inducing LHRH specific antibody response, in turn, inhibiting the reproductive capacity of the animal.

Ngo *et al*, of record, teach that the amino acid positions within the polypeptide/protein that can tolerate change such as conservative substitution or no substitution, addition or deletion

which are critical to maintain the protein's structure/function will require guidance (See Ngo et al., 1994, The Protein Folding Problem and Tertiary Structure Prediction, pp. 492-495).

Kuby *et al*, of record, teach that immunizing a peptide versus a full-length protein may result in **antibody specificity** that differs from antibody specificity directed against the native full-length polypeptide. Without the specific amino acid residues, it is unpredictable which undisclosed LHRH-conjugate in a composition would generate antibody that has the binding specificity for LHRH. In the absence of guidance as to what alterations would result in LHRH-diphtheria toxoid conjugate that retains the same functions and generating antibody having the same binding specificity as antibody to LHRH, it would require undue experimentation of one skilled in the art to practice the claimed invention. See page 1338, footnote 7 of Ex parte Aggarwal, 23 USPQ2d 1334 (PTO Bd. Pat App. & Inter. 1992).

Abaza *et al*, of record, teach that even a single amino acid substitution outside the antigenic site can exert drastic effects on the reactivity of a protein with monoclonal antibody against the site (See abstract, in particular).

Singh *et al* teach that azotization at histidine and or tyrosine of GnRH and conjugated to carrier protein such as BSA, the immunoreactivity of GnRH/azo-GnRH towards monoclonal and polyclonal antibodies was drastically hampered after conjugation (See abstract, in particular).

Bowers *et al* teach various LHRH analogs. Bowers et al further teach that it is unpredictable which analog that has in vitro effects correlates with in vivo effects. "The most potent inhibitors of ovulation were always very potent in vitro, but other analogs having identical in vitro activities had little or no antiovulatory activity even at substantially higher dosages. Further, the analogs inhibited the action of LHRH in the rat more easily than in the chimpanzee (See abstract, in particular).

Given the indefinite number of undisclosed derivatives, it is unpredictable which undisclosed derivative in the claimed composition would be effective for eliciting LHRH specific antibody immune response in turn, has contraceptive functions.

For these reasons, it would require undue experimentation of one skilled in the art to practice the claimed invention. See page 1338, footnote 7 of Ex parte Aggarwal, 23 USPQ2d 1334 (PTO Bd. Pat App. & Inter. 1992).

In re wands, 858 F.2d at 737, 8 USPQ2d at 1404 (Fed. Cir. 1988), the decision of the court indicates that the more unpredictable the area is, the more specific enablement is necessary. In view of the quantity of experimentation necessary, the limited working examples, the

unpredictability of the art, the lack of sufficient guidance in the specification and the breadth of the claims, it would take an undue amount of experimentation for one skilled in the art to practice the claimed invention.

Applicant's arguments filed 10/15/03 have been fully considered but are not found persuasive.

Applicant's position is that (1) LHRH is a 10 amino acids that corresponds to a single epitope only defined by 5 contiguous C-terminal amino acids of SEQ ID NO: 1. Thus only six LHRH forms comprise this genus (the 1-10, 2-10, 3-10, 4-10, 5-10 and 6-10 forms). Applicant submits that as a result of the small size of LHRH, Kuby and Abaza do not raise applicable issues in regard to the claimed compositions. Since sequence listings for each of the three out of the six LHRH forms are described in the specification, the enablement requirement is satisfied. (2) With regard to the LHRH derivatives, applicant amended the claims to recite "an amino acid sequence at least 5 contiguous amino acids of the C-terminal end of SEQ ID NO: 1 or derivative thereof". "Derivatives" as recited in the claims connotes fragments, parts, or portions from natural, synthetic or recombinant sources, including amino acid insertion, deletion, or substitution. The methods of making and using a modified LHRH based on the acceptable amino acid substitution is provided in the Table 1.

However, the structure such as the amino acid sequence of the LHRH derivative such as insertions could be any sequence of any length so long it contains at least 5 contiguous amino acids of the C-terminal end of SEQ ID NO: 1. Further, the term "comprises" is open-ended. It expands the LHRH fragment in the claimed composition to include additional amino acids at either or both ends. There is insufficient guidance as to which undisclosed amino acids to be added, or substituted and whether the resulting LHRH derivative has the same secondary and tertiary structure as SEQ ID NO: 1. Without the specific amino acid sequence, one of skill in the art cannot make, much less use the derivative in the claimed composition and pharmaceutical composition for inducing antibody response that is specific to LHRH for inhibiting the reproductive capacity of the animals. With regard to claim 66, even if the derivative wherein the LHRH is up to 10 amino acids in length and "comprises" its C-terminal end 5 contiguous amino acids of SEQ ID NO: 1, there is insufficient guidance what are the "component" in the LHRH that is conjugated to dipheria toxoid and absorbed to an ionic polysaccharide in the claimed composition. Since the "component" in the claimed composition is not enabled, it follows that any composition mentioned above where ionic polysaccharide is DEAE dextran, or wherein said

LHRH is SEQ ID NO: 1, 2, 3, or 4 is not enabled. With regard to claim 78, there is insufficient guidance for the other amino acids in the LHRH amino acid sequence so long the LHRH amino acid sequence is 5 contiguous amino acids of the C-terminal end of SEQ ID NO: 1 in the claimed composition. Let alone inducing any immune response to LHRH, in turn, effective for inhibiting the reproductive capacity of the animals. As to claims 80-83, since the LHRH derivatives are not enabled, it follows that the spacers and at least one amino acid substitution according to table I in the claimed composition is not enabled. Even if the LHRH derivative is defined, it is not clear as to what "spacers" are being claimed. The specification discloses only SEQ ID NO: 4 is a derivative of SEQ ID NO: 2 wherein the specific spacers have been introduced at the N-terminus (page 5, lines 22-23). Further, there are insufficient in vivo working examples demonstrating that any composition or pharmaceutical composition comprising any derivative of LHRH mentioned above is effective for inducing LHRH specific antibody response, in turn, inhibiting the reproductive capacity of the animal.

5. Claims 1-8, 62-71, and 78-83 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor, at the time the application was filed, had possession of the claimed invention.

The specification does not reasonably provide a **written description** of (1) *any* composition or (2) *any* pharmaceutical composition for use in eliciting an effective immune response to LHRH said composition comprising *any* LHRH such as (3) *any* LHRH wherein the LHRH is *any* amino acid sequence at least 5 contiguous amino acids of the C-terminal end of SEQ ID NO: 1, (4) *any* "derivative thereof" such as derivatives "comprise" fragments and amino acid substitutions, insertions or deletions of any LHRH that is at least 5 contiguous amino acids of the C-terminal end of SEQ ID NO: 1, and (5) *any* LHRH up to 10 amino acids in length and comprises at its C-terminal end 5 contiguous amino acids of the C-terminal end of SEQ ID NO: 1, *any* LHRH derivative comprises spacers introduced at the N-terminus, or *any* LHRH derivative comprises at least any one amino acid substitution according to Table I for inducing antibody immune response to LHRH for contraception (inhibits the reproductive capacity of the animal).

The specification discloses only a composition or a pharmaceutical composition comprising a LHRH conjugated to diphtheria toxoid and adsorbed to an ionic polysaccharide wherein said LHRH is an amino acid sequence of at least five contiguous amino acids of the C

terminal end of SEQ ID NO: 1 selected from the group consisting of SEQ ID NO: 2, SEQ ID NO: 3, SEQ ID NO: 4 for antibody immune response to LHRH for contraception (inhibits the reproductive capacity of the animal). The specification discloses SEQ ID NO: 4 is a derivative of SEQ ID NO: 2 wherein spacers have been introduced at the N-terminus (page 5, lines 22-23). The specification defines derivatives on page 5 to include any fragments, parts, portions, chemical equivalents, mutants, homologs, analogs from natural, synthetic or recombinant source and fusion proteins...chemical equivalents may not necessary derived from LHRH but may share certain similarities.

Other than the specific LHRH peptide selected from the group consisting of SEQ ID NO: 1-4 mentioned above conjugated to diphtheria toxoid and absorbed to an ionic polysaccharide in the claimed composition for inducing antibody response to LHRH as contraceptive vaccine to inhibit the reproductive function of the animal, there is inadequate written description about the structure associated with function of *any* LHRH derivative mentioned above because the LHRH derivative such as insertions could be any sequence of any length so long it contains at least 5 contiguous amino acids of the C-terminal end of SEQ ID NO: 1. Further, the term "comprises" is open-ended. It expands the LHRH fragment in the claimed composition to include additional amino acids at either or both ends. There is written description about which undisclosed amino acids to be added, or substituted, and any combination of substitution, deletion, and/or addition and whether the resulting LHRH derivative has the same secondary and tertiary structure as SEQ ID NO: 1, in turn, useful for inducing LHRH specific antibody response.

With regard to claim 66, even if the derivative wherein the LHRH is up to 10 amino acids in length and "comprises" its C-terminal end 5 contiguous amino acids of SEQ ID NO: 1, there is inadequate written description about the "component" in the LHRH that is conjugated to dipheria toxoid and absorbed to an ionic polysaccharide in the claimed composition. Since the "component" in the claimed composition is not enabled, it follows that any composition mentioned above where ionic polysaccharide is DEAE dextran, or wherein said LHRH is SEQ ID NO: 1, 2, 3, or 4 is not enabled.

With regard to claim 78, there is inadequate written description about the other amino acids in the LHRH amino acid sequence so long the LHRH amino acid sequence is 5 contiguous amino acids of the C-terminal end of SEQ ID NO: 1 in the claimed composition. Let alone inducing any immune response to LHRH, in turn, effective for inhibiting the reproductive capacity of the animals.

As to claims 80-83, since the LHRH derivatives are not enabled, it follows that the spacers and at least one amino acid substitution according to table I in the claimed composition is not enabled. Even if the LHRH derivative is defined, it is not clear as to what "spacers" are being claimed. The specification discloses only SEQ ID NO: 4 is a derivative of SEQ ID NO: 2 wherein the specific spacers have been introduced at the N-terminus (page 5, lines 22-23).

Finally, the specification discloses only four modified form of LHRH represent by SEQ ID NO: 1-4 wherein the LHRH is from human only. Given the lack of a written description of *any* additional representative species of LHRH derivative, one of skill in the art would reasonably conclude that the disclosure fails to provide a representative number of species to describe the genus. Thus, Applicant was not in possession of the claimed genus. *See University of California v. Eli Lilly and Co. 43 USPQ2d 1398.*

Applicant is directed to the Revised Interim Guidelines for the Examination of Patent Applications Under the 35 U.S.C. 112, ¶ 1 "Written Description" Requirement, Federal Register, Vol. 66, No. 4, pages 1099-1111, Friday January 5, 2001.

Applicant's arguments filed 10/15/03 have been fully considered but are not found persuasive.

Applicant's position is that (1) LHRH is a well-defined molecule conserved across all mammals and is only 10 amino acids in length. Contrary to the examiner's assertions, the genus of LHRH compositions that comprise "an amino acid sequence of at least 5 contiguous amino acids of the C-terminal end of SEQ ID NO: 1" as recited in the claimed is limited. (2) The specification discloses that a peptide consisting of amino acids 1 to 10, 2 to 10, or 3 to 10 of the peptide described in SEQ ID NO: 1-4 is advantageous for preparing an LHRH composition comprising diphtheria toxoid and an ionic polysaccharide. The specification discloses that LHRH C-terminal fragments comprising at least five amino acids are suitable for use in the present invention. (3) Claims have been amended to recite LHRH derivative is now limited to fragments of LHRH and to amino acid substitutions, deletions, and additions of a LHRH sequence.

However, there is inadequate written description about the structure associated with function of *any* LHRH derivative mentioned above because the LHRH derivative such as insertions could be any sequence of any length so long it contains at least 5 contiguous amino acids of the C-terminal end of SEQ ID NO: 1. Further, the term "comprises" is open-ended. It expands the LHRH fragment in the claimed composition to include additional amino acids at either or both ends. There is written description about which undisclosed amino acids to be

added, or substituted, and any combination of substitution, deletion, and/or addition and whether the resulting LHRH derivative has the same secondary and tertiary structure as SEQ ID NO: 1, in turn, useful for inducing LHRH specific antibody response.

With regard to claim 66, even if the derivative wherein the LHRH is up to 10 amino acids in length and "comprises" its C-terminal end 5 contiguous amino acids of SEQ ID NO: 1, there is inadequate written description about the "component" in the LHRH that is conjugated to dipheria toxoid and absorbed to an ionic polysaccharide in the claimed composition. Since the "component" in the claimed composition is not enabled, it follows that any composition mentioned above where ionic polysaccharide is DEAE dextran, or wherein said LHRH is SEQ ID NO: 1, 2, 3, or 4 is not enabled.

With regard to claim 78, there is inadequate written description about the other amino acids in the LHRH amino acid sequence so long the LHRH amino acid sequence is 5 contiguous amino acids of the C-terminal end of SEQ ID NO: 1 in the claimed composition. Let alone inducing any immune response to LHRH, in turn, effective for inhibiting the reproductive capacity of the animals.

As to claims 80-83, since the LHRH derivatives are not enabled, it follows that the spacers and at least one amino acid substitution according to table I in the claimed composition is not enabled. Even if the LHRH derivative is defined, it is not clear as to what "spacers" are being claimed. The specification discloses only SEQ ID NO: 4 is a derivative of SEQ ID NO: 2 wherein the specific spacers have been introduced at the N-terminus (page 5, lines 22-23).

Finally, the specification discloses only four modified form of LHRH represent by SEQ ID NO: 1-4 wherein the LHRH is from human only. Given the lack of a written description of *any* additional representative species of LHRH derivative, one of skill in the art would reasonably conclude that the disclosure fails to provide a representative number of species to describe the genus. Thus, Applicant was not in possession of the claimed genus. *See University of California v. Eli Lilly and Co. 43 USPQ2d 1398.*

6. Claims 66-77 are rejected under 35 U.S.C. 112, first paragraph, containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. **This is a new matter rejection.**

The "up to 10 amino acids in length" in Claims 66 and 72 represents a departure from the specification and the claims as originally filed. The passages pointed out by applicant in the amendment filed 10/15/03 do not provide a clear support for the said phrase.

7. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 103(a) that form the basis for the rejections under this section made in this Office Action:

A person shall be entitled to a patent unless:
(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

8. Claims 1, 2, 5-6, 62, 66-68, 72-74, 78 and 79 are rejected under 35 U.S.C. 103(a) as being unpatentable over WO 88/05308 publication (July 1988, PTO 892) in view of Talwar *et al* (Int J Immunopharmacol 14(3): 511-4, April 1992, PTO 892) and Kaistha et al, Indian J Pathiol Microbiol 39(4): 287-92, Oct 1996.

The WO 88/05308 publication teaches a pharmaceutical composition for eliciting an effective antibody immune response to LHRH wherein the reference composition comprises a LHRH having an amino acid sequence of at least 5 contiguous amino acids of the C-terminal end of SEQ ID NO: 1 such as LHRH (1-10) which is identical to claimed SEQ ID NO: 1 or LHRH derivative such as LHRH (4-10) and LHRH (5-10) fragments (deletion of LHRH) that have 5 contiguous amino acids Gly-Leu-Arg-Pro-Gly identical to the 5 contiguous amino acids of C-terminal end of SEQ ID NO: 1 conjugated to a carrier protein such as bovine serum albumin and absorbed to immunoadjuvant such as polycationic, polyanionic polyelectrolyte and mineral oil and a pharmaceutical acceptable carrier such as saline (See page 17, page 8, lines 19-20, abstract, claims 1-5 of WO 88/05308 publication, page 7, lines 19-22, page 14, lines 24, in particular). The WO 88/05308 publication further teaches the reference composition is useful for inducing antibody response to LHRH for inhibiting the reproductive function of livestock (See page 8, lines 1-10, in particular).

The claimed invention in claim 1 differs from the teaching of the reference only that the composition wherein the LHRH is conjugated to diphtheria toxoid and adsorbed to an ionic polysaccharide.

The claimed invention in claim 5 differs from the teaching of the reference only that the pharmaceutical composition wherein the LHRH is conjugated to diphtheria toxoid and adsorbed to an ionic polysaccharide.

The claimed invention in claims 2, 67, and 73 differs from the teaching of the reference only that

Talwar *et al* teach a vaccine composition comprising LHRH (also known as GnRH) conjugated to carrier such as diphtheria toxoid and that the reference LHRH conjugated to diphtheria is effective as vaccine for control fertility (See abstract, in particular). The reference diphtheria toxoid carrier enhances antibody titers to LHRH (See abstract, in particular).

Kaistha *et al* teach that ionic polysaccharide such as DEAE-Dextran (DD) in a vaccine has adjuvant effect and significantly improve the immunogenicity of the reference vaccine by increase immune response (abstract, in particular).

Therefore, it would have been obvious to one of ordinary skill in the art at the time the invention was made to substitute the protein carrier BSA and the adjuvant in the reference conjugate as taught by the WO 88/05308 publication for the diphtheria toxoid carrier as taught by Talwar *et al* and the adjuvant DEAE-dextran as taught by the '487 patent, '586 patent and/or Kaistha et al. From the combined teachings of the references, it is apparent that one of ordinary skill in the art would have had a reasonable expectation of success in producing the claimed invention.

One having ordinary skill in the art would have been motivated to do this because Talwar *et al* teach that diphtheria toxoid carrier enhances antibody titers to LHRH (See abstract, in particular). Kaistha *et al* teach that ionic polysaccharide such as DEAE-Dextran (DD) in a vaccine has adjuvant effect and significantly improve the immunogenicity of the reference vaccine by increase immune response (abstract, in particular).

9. Claims 63, 65, 70, 76 and 80-83 are rejected under 35 U.S.C. 103(a) as being unpatentable over WO 88/05308 publication (July 1988, PTO 892) in view of Talwar *et al* (Int J Immunopharmacol 14(3): 511-4, April 1992, PTO 892) and Kaistha *et al*, Indian J Pathiol Microbiol 39(4): 287-92, Oct 1996 as applied to claims 1, 2, 5, 62, 66-68, 72-74, and 78 mentioned above and further in

view of Sad *et al* (of record, Immunology74: 223-227 (1991, PTO 892) or 5,378,688 (of record, Jan 1995, PTO 892) or EP0156280A2 patent (March 1985, PTO 892).

The combined teachings of the WO 88/05308 publication, Talwar *et al* and Kaistha *et al* have been discussed supra.

The claimed invention in claims 63, 65, 70, and 76 differs from the teaching of the combined reference only that the composition wherein the LHRH is SEQ ID NO: 3.

The claimed invention in claims 80-81 differs from the teaching of the combined reference only that the composition wherein the LHRH derivative comprises spacers introduced at the N-terminus.

The claimed invention in claims 82-83 differs from the teaching of the reference only that the composition wherein the LHRH derivative comprises at least one amino acid substitution.

Sad *et al* teach a pharmaceutical composition comprising a GnRH, also known as LHRH, conjugated to diphtheria toxoid (DT) in alumn (See page 224, column 1, first three full paragraphs, in particular). The reference GnRH is a decapeptide (full length), which includes the claimed LHRH fragment of at least five amino acids of the C terminal of LHRH having at least one amino acid substitution containing Lysine instead of Glycine at position 6 (See page 223, column 2, Material and Methods, in particular). The term "comprising" is open-ended. It expands the claimed LHRH derivative to include the reference derivative. The reference LHRH derivative is useful for inducing GnRH specific antibody response (See Figure 2, in particular).

The '688 patent teaches a pharmaceutical composition comprising a LHRH-diphtheria toxin conjugate for a contraceptive vaccine (See column 5, last paragraph bridging column 6, first paragraph, Claim 1 of '688 patent, in particular). The '688 patent teaches modified form of LHRH or analog such as the ones in Table on column 5, and a method of making said LHRH conjugate (See column 16, last paragraph, in particular). The reference GnRH is a decapeptide (full length), which includes the claimed LHRH fragment of at least five amino acids of the C terminal of LHRH having at least one amino acid substitution containing D-NaphthylAla at position 6 of claimed SEQ ID NO: 1. The term "comprising" is open-ended. It expands the claimed LHRH derivative to include the reference derivative. The reference GnRH derivative is useful for a vaccine to sterilize mammals (inhibiting reproductive function) of mammals (See summary of '688 patent, Table in column 5, in particular).

The EP0156280A2 patent teaches LHRH (GnRH) derivative such as U-Trp-Ser-Tyr-Gly-Leu-Arg-Pro-Gly that is identical to the claimed SEQ ID NO: 3 (See page 6, line 19, in

particular). The EP0156280A2 patent teaches the reference LHRH derivative is a fragment of SEQ ID NO: 1 and contains at least one amino acid substitution such as Gly is substituted for Ser (See page 6, line 20, in particular). The reference LHRH derivative is useful for eliciting an immune response such as inhibiting steroid synthesis (See abstract, and claims of EP0156280A2 patent, in particular). The EP0156280A2 patent teaches spacer such as U or Pyr be introduced at the N-terminus (See abstract, in particular).

Therefore, it would have been obvious to one of ordinary skill in the art at the time the invention was made to substitute the LHRH in the reference conjugate as taught by the WO 88/05308 publication for the LRHR derivative as taught by Sad *et al* or the '688 patent or the EP0156280A2 patent teaches LHRH (GnRH) for a composition for eliciting an effective immune response to LHRH as taught by WO 88/05308 publication, Talwar *et al* and Kaistha *et al*. From the combined teachings of the references, it is apparent that one of ordinary skill in the art would have had a reasonable expectation of success in producing the claimed invention.

One having ordinary skill in the art would have been motivated to do this because Sad *et al* teach that the reference LHRH (GnRH) derivative is useful for inducing GnRH specific antibody response (See Figure 2, in particular). The '688 patent teaches that the reference LHRH or GnRH derivative is useful as a vaccine to eliciting an immune response such as sterilizing mammals (inhibiting reproductive function) of mammals (See summary of '688 patent, Table in column 5, in particular). The EP0156280A2 patent teaches that LHRH (GnRH) derivative such as U-Trp-Ser-Tyr-Gly-Leu-Arg-Pro-Gly is useful for eliciting an immune response such as inhibiting steroid synthesis (See abstract, and claims of EP0156280A2 patent, in particular). Claim 80 is included in this rejection because the EP0156280A2 patent teaches that LHRH (GnRH) derivative such as U-Trp-Ser-Tyr-Gly-Leu-Arg-Pro-Gly where the reference spacer is U at the N terminus of the reference GnRH.

10. Claims 3-4, 7-8, 69, 71, 75, and 77 are free of prior art.

11. Any inquiry concerning this communication or earlier communications from the examiner should be directed to "Neon" Phuong Huynh whose telephone number is (703) 308-4844. The examiner can normally be reached Monday through Friday from 9:00 am to 6:00 p.m. A message may be left on the examiner's voice mail service. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Christina Chan can be reached on (703) 308-3973. Any inquiry of a general nature or relating to the status of this application should be directed to the Technology Center 1600 receptionist (customer service) whose telephone number is (703) 872-9305.

12. Papers related to this application may be submitted to Technology Center 1600 by facsimile transmission. Papers should be faxed to Technology Center 1600 via the PTO Fax Center located in Crystal Mall 1. The faxing of such papers must conform to the notice published in the Official Gazette, 1096 OG 30 (November 15, 1989). The CM1 Fax Center telephone number is (703) 305-7401. The IFW official Fax number is (703) 872-9306. For After Final, the Fax number is (703) 872-9307.

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